Remarks

This paper is responsive to the Office Action dated September 30, 2004. In that Action, the Office rejected all of the pending claims, i.e., 41 and 58-63, as anticipated by Neri et al. (WO 97/40142). In response, Applicants respectfully submit the Office has erred in its interpretation of Neri et al. and that error produces an untenable rejection. To summarize, Neri et al. does not disclose a biopolymer having covalently linked calmodulin monomers.

Initially, Applicants note that claim 41 has been amended to incorporate the elements of claim 59, which depended from claim 58. Claims 58 and 59 have been canceled. Claim 59 had required that the biopolymer of claim 41 comprise a calmodulin dimer. As amended, claim 41 includes that requirement.

Turning now to the rejection, Applicants note that Neri et al. summarizes its technology at page 3, lines 24-30.

> According to the present invention, there is provided a ligand capable of binding a calcium dependent binding protein comprising an amino acid sequence corresponding to that of a wild type ligand for the calcium dependent binding protein, with a modification which results in enhanced affinity of the ligand for the calcium dependent binding protein.

Stated more simply, Neri et al. provide a modified ligand for a calcium-dependent binding protein. It is the ligand, not the calcium-dependent binding protein, that is the subject of Neri et al.'s disclosure.

Citing to page 8, lines 10-12, the Office asserts that Neri et al. teach the synthetic multimeric biopolymer of claim 41. In fact, at page 8, lines 10-12, Neri et al. describe how its "ligands . . . may be synthesized." (Page 8, line 10.) Note again that it is these ligands that bind to a calcium-dependent binding protein, and it is the ligands that Neri et al. is discussing. Thus, the Office asserts that Neri et al.'s ligands meet the limitations of Applicants' claim.

Citing to page 13, lines 16-25, the Office asserts that Neri et al.'s synthetic multimeric biopolymer comprises a plurality of monomeric units. Turning to the actual disclosure of Neri et

al., one sees that the multimers again referred to are the ligands. Thus, Neri et al. suggests, "[d]imeric peptide ligands could be used to dimerise recombinant calcium dependent binding protein fusion molecules." (Page 13, lines 18-20.) Here, Neri et al. seems to be suggesting that a ligand dimer (LD) would be able to bind to two calcium dependent binding proteins (CDBP), thereby creating a complex: CDBP-LD-CDBP. But this interaction between CDBP and LD is one of protein-ligand binding affinity, not covalent bonding. And it certainly cannot be said that a CDBP is covalently bonded to another CDBP.

Again relying on the same passage from Neri et al., the Office suggests that the described multimeric biopolymer comprises a binding region for an analyte. Here, it is entirely unclear what the Office sees as the analyte, as no guidance is given. Nothing in Neri et al. suggests that its multimeric biopolymer ligands comprise a binding region for an "analyte."

Applicants' claim recites that "each of the covalently linked monomeric units that comprise a binding region for an analyte generates a signal when the analyte is bound thereto; and [that] the signal generated by the covalently linked monomeric units that comprise a binding region for an analyte when the analyte is bound thereto is greater than the signal generated by the monomeric units that comprise a binding region for an analyte not covalently linked to each other when the analyte is bound thereto." For this element of the claim, the Office points to Neri et al.'s disclosure at pages 12, 13, and 14, where Neri et al. describes the production of fluorescein-labeled peptide ligands.

However, Applicants respectfully submit that Neri et al.'s examples do not show what the Office alleges. Neri et al. synthesized peptide ligands for calmodulin and fluorescently labeled the ligands with fluorescein. The ligands were modified by changing the position of the fluorescent modification, which resulted in 17 different peptide ligands. (Example 1; page 14, line 24 – page 15, line 19.) Example 2 (page 15, line 20 – page 16, line 12) allegedly shows the results of binding of the 17 peptides to calmodulin. The results show "that all the synthesized peptides bind to calmodulin in native PAGE gels, indicating that single alanine substitutions have no severely deleterious effect on calmodulin binding." (Page 16, lines 2-6.)

Example 3 (page 16, line 14 – page 10) describes the measurement of association, dissociation, and isomerization kinetics of the calmodulin-peptide binding interactions. As noted by Neri et al., peptide and calmodulin associate and dissociate in an interaction characterized by a first binding constant ($k_{+1/-1}$). (Page 16, lines 16-28.) The peptide-calmodulin complex then isomerizes according to a second constant ($k_{+2/-2}$). (*Id.*)

After extensively discussing the kinetics of the aforementioned binding and isomerization, Neri et al. notes that peptide 6 had enhanced binding affinity as compared to all other tested peptides, and additional experiments were performed. (Page 21, lines 24-25; et seq.) Despite all of Neri et al.'s analyses and discussion, there is no mention of any testing of monomeric units linked versus unlinked, or of a difference in signal generated by units linked covalently versus noncovalently. There is no support whatsoever for the Office's statement that Neri et al. discloses that "the signal generated by the monomeric units linked covalently with each other bound to an analyte is greater than the signal generated by the monomeric units that are linked noncovalently linked to each other and bound to an analyte." (Office Action, page 3, lines 7-9, citations omitted.)

Turning to rejecting claims 58 and 59, the Office asserts that Neri et al. disclose that the multimeric biopolymer comprises at least one calmodulin monomer or a dimer or multimer. (Office action, page 3, lines 12-13.) Note that previously in this Office Action, the Office had taken the position that Applicants' claimed multimeric biopolymer was anticipated by Neri et al.'s ligand; now the Office asserts that it is Neri et al.'s disclosure of calmodulin. Note that Neri et al.'s peptide ligands *bind to* calmodulin – the two cannot be the same.

Regardless of the Office's reasoning or arguments, Applicants respectfully submit that there is no disclosure in Neri et al. of a multimeric biopolymer comprising a calmodulin dimer wherein the multimers are covalently bonded together. As noted above, Neri et al. seems to suggest that a ligand dimer (LD) could bind to two calcium dependent binding proteins (CDBP), thereby creating a complex: CDBP-LD-CDBP. But again, this interaction between CDBP and LD is one of protein-ligand binding affinity, not covalent bonding. It cannot be said that a CDBP is covalently bonded to another CDBP.

For these reasons, Applicants respectfully submit that claim 41 is not anticipated by Neri et al. Claims 60-63 depend from claim 41, and for at least the above-described reasons, are also not anticipated by Neri et al.

Conclusion

Applicants respectfully submit that Neri et al. does not anticipate the claimed invention and Applicants respectfully request the prompt allowance of the application. If there are issues that can be resolved by telephone, the Office is invited to call Applicants' representative at the number shown below.

Respectfully submitted,

Date: December 29, 2004

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